

AD \_\_\_\_\_

Award Number: DAMD17-97-1-7111

TITLE: The Relationship Between Endocrine Factors and Breast  
Cancer Risk

PRINCIPAL INVESTIGATOR: Tanya D. Agurs-Collins, Ph.D.

CONTRACTING ORGANIZATION: Howard University  
Washington, DC 20059

REPORT DATE: September 2000

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20010424 073

**REPORT DOCUMENTATION PAGE**Form Approved  
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

**1. AGENCY USE ONLY (Leave blank)****2. REPORT DATE**

September 2000

**3. REPORT TYPE AND DATES COVERED**

Final (15 Aug 97 - 14 Aug 00)

**4. TITLE AND SUBTITLE**

The Relationship Between Endocrine Factors and Breast Cancer Risk

**5. FUNDING NUMBERS**

DAMD17-97-1-7111

**6. AUTHOR(S)**

Tanya D. Agurs-Collins, Ph.D.

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Howard University

Washington, DC 20059

**8. PERFORMING ORGANIZATION  
REPORT NUMBER****E-MAIL:**

tagurs-collins@fac.howard.edu

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

**10. SPONSORING / MONITORING  
AGENCY REPORT NUMBER****11. SUPPLEMENTARY NOTES****12a. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for public release; distribution unlimited

**12b. DISTRIBUTION CODE****13. ABSTRACT (Maximum 200 Words)**

The study was designed to examine the relationships between hyperinsulinemia, insulin like growth factor-1, central adiposity, maximal adult weight, physical fitness and breast cancer risk in postmenopausal African-American women. The study employed a case-control design (86 controls and 43 cases). Mean age was 67 years (age range 55 to 79 years). We did not find a relationship between IGF-1 concentrations and breast cancer. A logistic regression model was used to adjust for potential confounding variables and to determine those factors that influence breast cancer risk. Our study revealed that breast cancer risk was influenced by waist circumference (OR=1.166; 95% CI: 1.051,1.308), education (OR=1.286; 95% CI: 1.062,1.594), insulin levels (OR=1.031; 95% CI: 1.004,1.065), sex hormone binding globulin levels (OR=0.960; 95%CI: 0.929,0.989), levels of percent free estrogen (OR=0.006,0.001,0.106), and strenuous physical activity in high school that was greater than 5 hours per week (OR=0.231; 95% CI: 0.065,0.720). These results are consistent with previous studies that show a positive association between high waist circumference, hyperinsulinemia and breast cancer risk, and a protective effect of physical activity early in life and breast cancer risk. Our findings suggest that high levels of insulin and a high waist circumference may partially explain the increased breast cancer seen in postmenopausal African American women.

**14. SUBJECT TERMS**

Breast Cancer, Physical activity, Waist Circumference, Insulin-like growth factor-1.

**15. NUMBER OF PAGES**

12

**16. PRICE CODE****17. SECURITY CLASSIFICATION  
OF REPORT**

Unclassified

**18. SECURITY CLASSIFICATION  
OF THIS PAGE**

Unclassified

**19. SECURITY CLASSIFICATION  
OF ABSTRACT**

Unclassified

**20. LIMITATION OF ABSTRACT**

Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)  
Prescribed by ANSI Std. Z39-18  
298-102

## Table of Contents

Cover.....	1.
SF 298.....	2.
Table of Contents.....	3.
Introduction.....	4.
Body.....	4.
Key Research Accomplishments.....	5.
Reportable Outcomes.....	7.
Conclusions.....	7.
References.....	8.
Appendices.....	10.

## INTRODUCTION

The present study was designed to examine the relationships between central obesity, physical activity, hyperinsulinemia, insulin-like growth factor-1 (IGF-1), and breast cancer risk in postmenopausal African-American women. Specifically, this research is expected to show that central obesity is positively associated with increased levels of insulin, IGF-1 and risk for breast cancer. Additionally, we expect to show that increased levels of IGF-1 and maximal adult weight gain are positively associated with the risk for developing breast cancer and to determine the time period for the protective effect of physical activity on breast cancer risk.

## BODY

### **Task 1: Develop and finalize questionnaires for printing.**

Study questionnaires were developed and finalized in February 1998.

### **Task 2: Hiring and Training Staff**

The University approved two positions along with the position descriptions for a medical research assistant and a data manager in October 1997. The positions were advertised and potential candidates were interviewed in November and December 1997. Two persons were selected and started working on the project in January and February 1998. Thereafter, training was implemented regarding the study goals, objectives, protocols, responsibilities and study questionnaires.

### **Task 3: Recruitment of cases and controls: informed consent; data collection**

The research design is a case-control study of postmenopausal women who are 55 to 79 years of age. A prescreening questionnaire was developed and administered to potential participant to determine initial eligibility. After the patients met the prescreening criteria, they were given an appointment to determine final screening criteria. If the patients were eligible for the study, they participated in a one-hour data collection interview. Before the interview an approved informed consent was read and explained to all study participants. The Institutional Review Board approved the informed consent on October 1997. In February 1998, recruitment of patients began at the Howard University Mammography clinic.

The recruitment of women with breast cancer became an arduous task due to the study exclusion criteria. Since the study outcome measure was insulin-like growth factor (IGF-1), the study eliminated person who are diabetic and who are taking estrogen replacement therapy. In the African American population, the prevalence of Type II diabetes is very high among women. Also, it is becoming increasing difficult to find postmenopausal women who are not taking some form of estrogen replacement therapy. In an effort to increase participation of women with breast cancer, we began recruiting patients from the Georgetown University Medical Center in October 1998 and at the DC General Hospital in November 1999.

Approval from the Department of Defense for a no-cost extension was granted in August 1999.

**Task 4:**                    **Send plasma to laboratory for analysis; work with oncologist to determine primary breast cancer cases.**

Plasma samples were drawn into tubes containing ethylenediaminetetraacetic acid (ETA), separated by centrifugation and analyzed by the commercial laboratory Quest Diagnostics, Inc. The research team worked well with the medical oncologist and radiologist within the various institutions.

**Task 5:**                    **Data Entry**

All questionnaires were coded and entered into the software program "Microsoft Excel."

**Task 6:**                    **Data analysis: Final Report**

Data analysis was conducted using the statistical software SAS. The final report is completed.

## **PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT**

Tanya Agurs-Collins  
Lolanda Tappin  
Deana M. Manassaram  
Cheryl Wise

## **KEY RESEARCH ACCOMPLISHMENTS**

All cases were newly histologically confirmed primary breast cancer. Descriptive statistics reveal that 72% of the study participants were retired; 44% received < \$20,000 income per year; 30% married; 50% completed 12 years or less of high school /GED; 41% no longer smoked; and 28% currently drink alcohol. Waist circumference ( $p=.04$ ), body weight ( $p=.03$ ) and hyperinsulinemia ( $p=.01$ ) were positively associated with breast cancer risk ( $p=.01$ ). A logistic regression model was used to adjust for potential confounding variables and to determine those factors that influence breast cancer risk. Listed below are the study objectives and research findings after statistical adjustment.

- **To determine the relationship between central adiposity and breast cancer risk in postmenopausal women.**

We hypothesize that central obesity is positively associated with breast cancer risk in postmenopausal African American women. Our study revealed that a high waist circumference increased breast cancer risks (OR=1.166; 95%CI: 1.051,1.308). Several case-control studies support this finding suggesting that central adiposity is a predictor of breast cancer risk (1-3). They suggest that increased abdominal adiposity with weight gain during menopause is associated with alterations in ovarian hormone and in growth factors that may promote breast cancer cell growth (2). Alterations in ovarian hormone involve an

increased conversion of adrenal androgens to estrone, which is believed to increase breast cancer risk (3).

- **To determine the relationship between maximum adult weight gain and breast cancer risk.**

The results showed no relationship between maximum adult weight gain and breast cancer risk. Waist circumference was a better predictor of breast cancer risk.

- **To determine if central adiposity is associated with an increased IGF-1 in postmenopausal women with breast cancer.**

The results showed no association between waist circumference and IGF-1 concentrations in our sample.

- **To determine the relationship between hyperinsulinemia and breast cancer risk.**

We hypothesize that a high level of insulin is associated with breast cancer risk in postmenopausal African American women. Hyperinsulinemia was associated with increased breast cancer risk in this population. This finding supports other studies which suggest that hyperinsulinemia with insulin resistance was a significant marker of increased breast cancer risk (4,5). These studies suggest that hyperinsulinemia can increase breast cancer risk because of its association with decreased plasma levels of sex hormone binding globulin resulting in a rise of free estradiol and free testosterone (6). Another explanation is by raising the bioactive level of IGF-1 concentrations as a result of its regulation of IGF-binding protein production (7). Additionally, hyperinsulinemia was significantly related to maximum adult weight, body weight, waist circumference, and waist-hip-ratio.

- **To determine the relationship between IGF-1 and breast cancer risk.**

We were surprised to find no association between IGF-1 concentrations and breast cancer risk. This finding is consistent with results from a nested case-control study which did not find an association between circulating IGF-1 concentrations among postmenopausal women, but did find a significant positive association among premenopausal women who were less than 50 years old (8). However, more research needs to be done in this area. To date, only two case-control studies have found a positive association between IGF-1 concentrations and breast cancer risk (9,10)

- **To determine the relationship between physical activity and breast cancer risk.**

Our results revealed that strenuous physical activity in high school that was greater than 5

hours per week had a protective effect by decreasing one's risk from breast cancer by 77%. (OR=0.231; 95%CI: 0.065,0.720). Several studies have shown physical activity to have a protective effect from breast cancer (11-13), but not later in life (14). It is believed that physical activity modifies breast cancer risk through a hormone-related pathway (13). Also, persons who are physically active have a reduction in body fatness, improved glycemic control, improved insulin sensitivity, and a reduction in fasting hyperinsulinemia (15).

## **REPORTABLE OUTCOMES (see appendices)**

- June 8-11, 2000, an abstract of preliminary findings was presented at the Era of Hope, Department of Defense Breast Cancer Research Program Meeting in Atlanta, Georgia.
- On October 6, 2000, an abstract was submitted to the American Association For Cancer Research to be presented at the annual meeting in New Orleans, Louisiana, March 2001. If selected, the Department of Defense will be recognized as the funding source for this research.

## **CONCLUSIONS**

We examined the role of central adiposity, maximal adult weight gain, physical activity, hyperinsulinemia, insulin-like growth factor-1 (IGF-1) and their relationships to postmenopausal breast cancer risk among African American women. Our study revealed that breast cancer risk was associated with a high waist circumference and hyperinsulinemia. Also, we found that physical activity during high school was protective of breast cancer risk.

Few studies have addressed the issue of physical activity and breast cancer risk among postmenopausal women. Also, the literature is mixed with studies showing little evidence that physical activity later in life has a protective effect. Our study supports this finding revealing the protective efforts to occur early in life. Increased physical activity is believed to prevent breast cancer by reducing cumulative life time exposure to circulating ovarian hormones.

Research has shown that central obesity was associated with higher risk for breast cancer. Both central obesity and visceral obesity are associated with insulin resistance and hyperinsulinemia. Hyperinsulinemia is associated with both higher levels of IGF-1 and can determine the bioavailable of IGF-1 in tissues. Central adiposity and hyperinsulinemia are common side effects characterized by high caloric intake and decreased physical activity among postmenopausal women. Excess nutrition in the adult years, central adiposity and decrease physical activity in the early years of life may explain in part the increasing incidence of breast cancer among postmenopausal African American women.

Recommendations for future studies examining physical activity and breast cancer risk should take into consideration the type of and timing of physical activity as well as leisure-time exercise. Also, the relationship between IGF-1 and breast cancer risk in postmenopausal women needs to be clarified. Moreover, the hormonal and metabolic mechanisms that influence IGF-1 and breast cancer risk are not adequately understood and require further study.

Our research is unique in that few studies have examined physical activity,

hyperinsulinemia, waist circumference and IGF-1 levels among postmenopausal African American women. The study results contribute to the body of evidence suggesting that central adiposity, hyperinsulinemia and low levels of physical activity may increase breast cancer risk in postmenopausal women. Modifying these risk factors may have a profound public health impact on the incidence of breast cancer in women from various ethnic and racial backgrounds.

## REFERENCES

1. Ng EH, Gas F, Ji CY, Ho GH, Soo KC. Risk factors for breast carcinoma in Singaporean Chinese women: the role of central obesity. *Cancer* 15:725-31, 1997.
2. Ballard-Barbash R. Anthropometry and Breast Cancer: Body Size—A Moving Target. *Cancer*, 74:1090-1100, 1994
3. Folsom AR, Kay SA, Princeas RJ, Potter JD, Capstur SM, et al. Increased incidence of carcinoma of the breast associated with abdominal adiposity in post-menopausal women. *Amer J. Epidemiol*, 131:794-803, 1990.
4. Bruning BF, Bonfrer JMG, Van Noord PAH, Hart AAM, De Jong Bakker M, et. al. Insulin resistance and breast cancer risk. *Int J Cancer* 52, 511-516, 1992.
5. Gamayunova VB, Bobrov YF, Tsyrlina EV, Eukushenko TP, et al. Comparative study of blood insulin levels in breast and endometrial cancer. *Neoplasma* 44, 123-126, 1997.
6. Preziosi P, Barrett-Conner E, Papoz L, Roger M, Saint-Paul M et. al. Interrelation between plasma SHBG and insulin in healthy adult women. *J Clin Endocrinol Metab* 76, 283-287, 1993.
7. Cotterill A, Holly J, Savage M. The current status of the IGF's and their binding proteins. *Growth Matters* 9, 7-10, 1992.
8. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, et al. Circulating concentrations of insulin-like growth factor-1 and risk of breast cancer. *Lancet*, 351:1393-96, 1998.
9. Peyrat JP, Bonnetterre J, Hecquet B, Vennin P, Louchez MM, et. al. Plasma IGF-1 Concentrations in Human Breast Cancer . *Eur J Cancer*, 29A:492-497, 1993.
10. Agurs-Collins TD, Adams-Campbell LL, Kim KS, Cullen K. The relationship Between Insulin Growth Factor-1 and Postmenopausal Breast Cancer Among African American Women . *Cancer Detec Preven*, 24:199-206, 2000.



11. Dorgan JF, Brown C, Barrett M, Splansky GL, Kreger BE, et. Al. Physical activity and risk of breast cancer in the Framingham Heart Study. *Am J. Epidemiol*, 139:662-669, 1994.
12. Friedenreich CM, Rohan TE. Physical Activity and Risk of breast cancer. *Eur J. Cancer Prev.* 4:145-151, 1995.
13. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. *J Natl Cancer Inst*; 86:1403-1408,1994.
14. Moore DB, Folsom AR, Mink PJ, Hong CP, Anderson KE, Kushi LH. Physical activity and incidence of post-menopausal breast cancer. *Epidemiology* 11:292-6, 2000.
15. Richter EA, Turcotte L, Hespel P, Kiens B. Metabolic Response to Exercise. *Diabetes Care*, 15(Suppl 4) 1767-1776, 1992.

## **APPENDICIES**

## THE RELATIONSHIP BETWEEN ENDOCRINE FACTORS AND BREAST CANCER RISK

T. Agurs-Collins<sup>1</sup>, E. Duckett<sup>2</sup>, D. Manassaram<sup>1</sup>, K. Kim<sup>1</sup>, L. Adams-Campbell<sup>1</sup>

<sup>1</sup>Howard University Cancer Center, Washington, D.C.

<sup>2</sup>Howard University Hospital, Washington, D.C.

tagurs-collins@fac.howard.edu

We examined the relationships between central adiposity, maximal adult weight, physical activity, hyperinsulinemia, insulin-like growth factor (IGF-1) and breast cancer risk in postmenopausal African American women. The study has a case-control design, and thus far has recruited 118 women (87 control and 31 cases). Preliminary descriptive statistics reveal that 72% of the study participants were retired; 48% received < \$20,000 income per year; 31% were married; 52% completed 12 years or less of high school /GED; 44% no longer smoked; and 28% currently drink alcohol. We examined the relationships between body weight, central adiposity and breast cancer. Waist circumference ( $p=.02$ ) and body weight ( $p=.03$ ) were shown to be positively associated with breast cancer. However, waist-to-hip ratio and maximum adult weight were not significantly related to breast cancer. We did not find a relationship between IGF-1 concentrations and breast cancer. Also, IGF-1 concentrations, waist circumference and insulin concentrations were not related. However, hyperinsulinemia was positively associated with breast cancer ( $p=.04$ ) and waist-hip-ratio ( $p=.014$ ), but not with waist circumference. Sex hormone binding globulin concentrations were negatively associated with breast cancer ( $p=.02$ ). We examined the relationship between physical activity and breast cancer. Walking 2 to 4 hours per week ( $p=.02$ ) and strenuous physical activity during high school that was greater than 5 hours per week ( $p=.02$ ) were shown to be protective of breast cancer. A logistic regression model was used to adjust for potential confounding variables and to determine those factors that influence breast cancer risk. Our study revealed that breast cancer risk was influenced by body weight (OR=1.017; 95% CI:1.002,1.034), education (OR=1.394; 95% CI:1.113,1.803), walking 2 to 4 hours per week (OR=0.193; 95% CI:0.050,0.646) and strenuous physical activity in high school that was greater than 5 hours per week (OR=0.070; 95% CI:0.012,0.284). We are currently in our final year of recruiting breast cancer cases. A larger sample size may definitively determine the relationships between IGF-1, hyperinsulinemia, central adiposity and breast cancer risk in this population.

The U.S Army medical Research and Materiel Command under DAMD17-97-1-7111 supported this work.

## **Abstract Status**

We have successfully received your abstract, which is displayed below. Your abstract will be graded and then a decision will be made about whether to include it in the Program, and if so, where within the Program. You will receive notice via email when decisions have been made.

---

### **THE RELATIONSHIP BETWEEN HORMONES, WEIGHT, PHYSICAL ACTIVITY AND BREAST CANCER RISK**

Agurs-Collins, Tanya D; Kim, Kyungsook; Adams-Campbell, Lucile; Duckett, Eva; Manassaram, Dena  
Howard University Cancer Center, Washington DC

We examined the relationships between central adiposity, maximal adult weight, physical activity, hyperinsulinemia, insulin-like growth factor (IGF-1) and breast cancer risk in postmenopausal African American women. In a case-control design, 129 women (86 controls and 43 cases) with a mean age of 67 years were studied. Descriptive statistics reveal that 72% of the study participants were retired; 44% received < \$20,000 income per year; 30% married; 50% completed 12 years or less of high school /GED; 41% no longer smoked; and 28% currently drink alcohol. Waist circumference ( $p=.04$ ), body weight ( $p=.03$ ) and hyperinsulinemia ( $p=.01$ ) were positively associated with breast cancer risk. We did not find a relationship between IGF-1 concentrations and breast cancer. However, hyperinsulinemia was significantly related to maximum adult weight, body weight, waist circumference, and waist-hip-ratio. A logistic regression model was used to adjust for potential confounding variables and to determine those factors that influence breast cancer risk. Our study revealed that breast cancer risk was influenced by waist circumference (OR=1.166; 95% CI: 1.051,1.308), education (OR=1.286; 95% CI: 1.062,1.594), insulin levels (OR=1.031; 95% CI: 1.004,1.065), sex hormone binding globulin levels (OR=0.960; 95%CI: 0.929,0.989), levels of percent free estrogen (OR=0.006,0.001,0.106), and strenuous physical activity in high school that was greater than 5 hours per week (OR=0.231; 95% CI: 0.065,0.720). These results are consistent with previous studies that show a positive association between high waist circumference, hyperinsulinemia and breast cancer risk, and a protective effect of physical activity early in life and breast cancer risk. Our findings suggest that high levels of insulin and a high waist circumference may partially explain the increased breast cancer seen in postmenopausal African American women. A larger sample size may definitively determine the relationship between IGF-1 and breast cancer risk in this population.